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Perioperative Glucocorticoid Coverage

A Reassessment 42 Years After Emergence of a Problem

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Objective

The authors review the historical basis for the provision of perioperative glucocorticoid coverage, and detail the evolution in the understanding of the role of the hypothalamic-pituitary-adrenal cortical (HPA) axis in response to physical stressors. New recommendations are proposed for glucocorticoid-dependent patients who require anesthesia and surgery.

Summary Background Data

In 1952, a patient developed surgery-associated adrenal insufficiency as a result of preoperative withdrawal from glucocorticoid therapy. That case report, and one other in the ensuing 12 months, prompted the publication of recommendations for perioperative glucocorticoid coverage, which became the standard of care. The understanding of the role of the HPA axis in the stress response has been subsequently refined; however, recommendations for perioperative glucocorticoid coverage have not been altered in parallel.

Methods

Studies were identified beginning with the first reports of the physiologic actions of the adrenal glands (1855) and the description and clinical use of cortisone (1930–1993). Studies were selected for review if they were related to or evaluated the provision of stress-related glucocorticoid administration. All clinical studies were evaluated to determine the basis for the provision of perioperative glucocorticoid coverage and the validity of the data used to justify these conclusions.

Conclusions

Clinical and experimental evidence support the concept that the current amount of perioperative glucocorticoid coverage is excessive and has been based on anecdotal information. New recommendations are proposed which suggest that the amount and duration of glucocorticoid coverage should be determined by: a) the preoperative dose of glucocorticoid taken by the

patient, b) the preoperative duration of glucocorticoid administration, and c) the nature and anticipated duration of surgery.

HISTORICAL PERSPECTIVE

Forty-two years have passed since Fraser and colleagues described a patient who developed perioperative circulatory shock as a consequence of secondary adrenal insufficiency.[1] Although primary adrenal insufficiency had been known since the mid 19th century (Sir Thomas Addison's report of adrenal gland destruction by tuberculosis was published in 1855[2]), the concept of secondary adrenal insufficiency was not developed until nearly a century later. Cushing is credited for the conceptual association of pituitary and adrenal cortical function.[3,4] Over the next 20 years, Swingle and colleagues[5–9] showed that adrenalectomized dogs were predisposed to hypovolemic and laparotomy-induced circulatory shock; they also showed that this could be prevented by administering glucocorticoids.[9]

Although physiologic responses to adrenal medullary extracts had been evaluated by the beginning of the twentieth century,[10,11] it was not until 1930 that Swingle and Pfiffner showed that adrenal cortical extracts could maintain life in adrenalectomized animals.[12,13] Reichstein in Switzerland,[14,15] and Kendall in the United States[16,17] led the effort to isolate, characterize, and synthesize cortisone and other adrenal steroids, such as deoxycortisone. Swingle then showed that cortisol prevented the circulatory collapse associated with adrenalectomy.[8] In 1949, Hench and co-workers[18,19] described the beneficial effects of cortisone in patients with rheumatoid arthritis (Hench shared the Nobel Prize in medicine with Kendall and Reichstein for this contribution). The era of glucocorticoid therapy for diseases other than primary adrenal insufficiency began with this finding.

In 1952, Fraser and co-workers described the first (reported) patient who developed surgery-associated adrenal insufficiency as a consequence of preoperative withdrawal from glucocorticoid therapy.[1] The following year, Lewis and colleagues[20] described a similar patient who died several hours after surgery had been performed to repair a flexion contracture of the right knee. The patient had chronic disabling rheumatoid arthritis, and had been receiving cortisone daily for 5 months before the knee surgery. The cortisone was discontinued the day before surgery. A postmortem examination revealed diffuse atrophy and hemorrhage in the adrenal glands. The case report concluded with a list of recommendations for perioperative glucocorticoid treatment, which became the standard of therapy for perioperative glucocorticoid coverage.[20] Those recommendations, amounting to roughly a fourfold increase in glucocorticoid administration, have been generalized so that the current dose of glucocorticoids is quadrupled routinely. For example, a patient receiving 50 mg of prednisone daily for chronic obstructive pulmonary disease can receive 200 mg of prednisone daily during the perioperative period. This is equivalent to 1000 mg of cortisol each day. For the sake of perspective, it is worth noting that the average cortisol production rate in patients with Cushing's syndrome is 36 mg/day.[21] This excess of glucocorticoid leads to adverse clinical consequences, such as reduced tissue repair rates, decreased glucose tolerance, and increased susceptibility to infection caused by immune compromise. Knowledge of adrenal cortical responses to physical stressors has been refined over the past 20 years.[22–26] As a consequence, perioperative glucocorticoid management can be prescribed in a more rational fashion.

This article considers the following issues: 1) evidence supporting the need for perioperative glucocorticoid coverage; 2) identifying patients needing coverage; 3) and prescribing guidelines for perioperative coverage.

THE NEED FOR PERIOPERATIVE GLUCOCORTICOID COVERAGE

The hormonal responses to surgery,[22–25] critical illness, and trauma[26–29] have been studied extensively over the past 20 years. Plasma adrenocorticotropic hormone (ACTH)[30–31] and cortisol concentrations,[22,32–36] urinary-free cortisol,[37,38] and the concentrations of urinary metabolites of cortisol[39,40] increase in response to surgery, trauma, and other forms of critical illness.[26,41] There is considerable inter-individual variation in the hypothalamic-pituitary-adrenal cortical (HPA) response to surgical stress.[23] Some of the variation can be attributed to the actions of anesthetics,[23,42,43] exogenous and endogenous[44] opiate analgesics (administered intrathecally,[45] epidurally,[46] or parenterally[47]), antihypertensive agents,[48] age,[49] sleep,[50] and infection.[51] All of these factors can alter the HPA response to surgery and other stresses. In addition, the pulsatile secretory patterns of ACTH and cortisol[52] contribute to the apparent variability in the measured responses to surgical stress.

Perioperative adrenal insufficiency is an excellent model for studying stress-associated adrenal crisis. It is an uncommon complication of surgery. Mohler and colleagues[53] noted only one case of perioperative adrenal

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Table 1. CLINICAL DATA IN GLUCOCORTICOID TREATED PATIENTS IN WHOM POSTOPERATIVE DEATH OR HYPOTENSION WAS PUTATIVELY SECONDARY TO STRESS-INDUCED ADRENOCORTICAL INSUFFICIENCY*

Authors	No. of Cases	Interval between Surgery and Shock or Death (hrs)	Plasma Cortisol (mmol/L)	Supplementary Glucocorticoids	Comments and Observations on the Diagnosis of Acute Stress-Induced Adrenal Insufficiency
Fraser et al. (1952)	1	3	—	No	Inconclusive, fever, dyspnea, death after transfusion, anaphylactic reaction?
Lewis et al. (1953)	1	6	—	No	Not rejected, no biochemical evidence
Salassa et al. (1953)	1	30	—	Yes	Inconclusive, death
Salassa et al. (1953)	1	16	—	No	Not rejected, no biochemical evidence
Downs and Cooper (1955)	1	14	—	Yes	Inconclusive, perforated ulcer, death
Dragsted et al. (1955)	2	8 and 30	—	No	Inconclusive, sudden death
Kittredge (1955)	1	48	—	Yes	Inconclusive, sudden death
Allanby (1957)	1	20	—	No	Inconclusive, perforated colon, death
Kern (1957)	1	23	—	No	Inconclusive, death
Sloynay and Brooke (1957)	1	13	—	No	Inconclusive, death
Winstone and Brooke (1961)	1	24	—	No	Inconclusive, ulcerative colitis, death
Haller and Kirchoff (1963)	1	36	—	No	Inconclusive, death
Downs and Cooper (1955)	1	2	—	No	Inconclusive, hypotension
Marnegel and Kramer (1955)	1	12	—	No	Inconclusive, hypotension
Nicholas et al. (1955)	1	1	—	Yes	Inconclusive, hypotension
Hayes and Kushlan (1956)	4	Preoperative	—	No	Inconclusive, hypotension
Hayes (1956)	5	Preoperative	—	No	Inconclusive, hypotension
Hayes (1956)	6	Preoperative	—	Yes	Inconclusive, hypotension
Howland et al. (1956)	1	Preoperative	—	No	Inconclusive, hypotension
Richman et al. (1956)	1	—	—	No	Inconclusive, hypotension
De Mowbroy (1957)	1	—	—	Yes	Inconclusive, hypotension
Dundee (1957)	2	2 and preoperative	—	Yes	Inconclusive, hypotension
Nicholas et al. (1957)	3	Postoperative	—	Yes	Inconclusive, hypotension
Sloynay and Brooke (1957)	1	12	—	Yes	Inconclusive, hypotension
Sloynay and Brooke (1957)	3	Postoperative, 6, 24	—	No	Cannot be rejected, hypotension
Gillies (1958)	1	Preoperative	—	Yes	Inconclusive, hypotension
Gillies (1958)	1	Preoperative	—	No	Inconclusive, hypotension
Marks et al. (1959)	1	2	390	No	Not adrenal insufficiency, hypotension
Marks et al. (1959)	1	24	520	Yes	Not adrenal insufficiency, hypotension
Clin Anes Conf (1961)	1	24	—	Yes	Inconclusive, hypotension
Sampson et al. (1961)	1	Preoperative	140	No	Fulfill diagnostic criteria of adrenal insufficiency, hypotension
Sampson et al. (1962)	1	Preoperative	140	No	Inconclusive, hypotension
Salem and Lund (1962)	1	Preoperative	—	No	Inconclusive, hypotension
Salem and Lund (1962)	1	Preoperative	—	No	Inconclusive, hypotension
Kaalund et al. (1966)	3	Preoperative and postoperative	—	Yes	Inconclusive, hypotension
Jansani et al. (1968)	1	Preoperative	170	No	Fulfill the diagnostic criteria
Kehlet and Binder (1973)	1	Preoperative	60	No	Fulfill the diagnostic criteria

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insufficiency (0.01%) in 6947 urologic surgical procedures. Five cases (0.1%) of adrenal insufficiency were found in 4346 cardiac surgical procedures.[54] In a series of 62,473 anesthetic administrations, glucocorticoid coverage was required in 419 cases (0.7%).[55] Only 3 episodes (0.7%) of hypotension due to inadequate glucocorticoid coverage were noted.

Kehlet has reviewed[23] the reported instances of death and hypotension (Table 1) attributed to perioperative adrenal insufficiency in glucocorticoid-treated patients. Although the majority of the early cases were inconclusive and lacked biochemical confirmation of adrenal insufficiency, Kehlet's data support the concept that the problem is real and *does* occur. In fact, a number of glucocorticoid-treated patients have undergone major surgery without perioperative glucocorticoid coverage or their usual baseline therapeutic dose of glucocorticoid.[33,54,56,57] Most of these patients had uneventful surgical courses. The likely explanation for this paradox is that most of these patients had normal preoperative bio-

chemical indices of HPA axis function, suggesting the unreliability of the historical assessment of glucocorticoid administration. Some of the patients from these series had documented HPA axis dysfunction (i.e., an inadequate plasma cortisol response to insulin-induced hypoglycemia or ACTH administration). Several of these patients developed perioperative hypotension. The small sample size and the limited longitudinal data provided prevent further analysis.[33,56,57] Our combined clinical experience and research findings, however, lead us to conclude that 1) clinicians need to replace glucocorticoids only in an amount equivalent to the normal physiologic response to surgical stress,[22,24,25] and 2) the risk of anesthetizing and operating on unsupplemented glucocorticoid-treated patients (prolonged use preoperatively, but none given intraoperatively) is dependent on the duration and severity of the surgery. The HPA axis response to minor surgery (defined arbitrarily as operations performed under local anesthesia and of less than 1 hour duration) is so minimal[22,36,40] that replacement therapy beyond the patient's normal glucocorticoid dosage seems unnecessary and potentially detrimental.

In support of these conclusions, one of us (J.B. and his co-workers) prospectively studied 40 renal allograft recipients (receiving 5–10 mg prednisone/day, long term) who required readmission to the hospital for operation or acute illness.[58] Blood samples for serum cortisol and ACTH, and "24-hour urine" collections for free cortisol determinations were obtained during the first 36 hours of hospitalization. An ACTH stimulation test was performed in 38 of the 40 patients at a later time, before discharge, when the patients were not acutely ill. The ACTH stimulation tests were abnormal in 63% of the patients. Ninety-seven per cent of patients, however, had normal or increased urinary cortisol concentrations, suggesting that circulating cortisol concentrations were sufficient to meet the patients' requirements during the time of stress.[58] There were 12 episodes of hypotension or hyponatremia. All patients responded promptly to treatment other than glucocorticoid administration. Each episode was explained readily by processes other than adrenal insufficiency. Throughout the hospitalization, none of these 40 patients received more than their baseline glucocorticoid therapy (5–10 mg prednisone/day).

These data suggest that baseline glucocorticoid therapy is sufficient to prevent adrenal insufficiency in the perioperative or stressful period. Similar to patients receiving prolonged glucocorticoid therapy, a large percentage of renal allograft recipients have biochemical evidence (i.e., an ACTH stimulation test) of inadequate adrenal reserve; nonetheless, supraphysiologic (stress) doses of glucocorticoids appear to be unnecessary. The point needs confirmation by larger studies. The preliminary data, however, are persuasive.

ASSESSMENT OF HPA FUNCTION

The degree of HPA dysfunction depends on the amount and duration of prior glucocorticoid therapy. Medication histories, however, are notoriously inaccurate.[23,33,36,60–63] Thus, assessment of the functional states of the HPA axis must be based on laboratory determinations. Because of the episodic nature of human cortisol secretion,[52,63] its circadian rhythm,[48] and the variability of the HPA axis response to stress,[23,64] single measurements of plasma cortisol, unless they are high, inadequately define the state of the HPA axis. A single plasma cortisol concentration of greater than 500 nmol/L is a strong argument for adequate HPA axis function. Most random plasma cortisol concentrations in normal subjects, however, are less than this value. Thus, to ensure that the plasma cortisol value reflects adrenal competence, a maximally stimulated value is essential.

The available provocative tests measure the plasma cortisol response to the administration of ACTH, corticotropin releasing hormone (CRH), pyrogen, lysine vasopressin, metyrapone, and insulin-induced hypoglycemia. Kehlet[23] states that the insulin tolerance and pyrogen tests are the "true stress" tests because their sites of stimulation are central. The intravenous administration of regular insulin (0.10–0.15 units/kg) results in a rapid (10–20 minutes to nadir in glucose) lowering of blood glucose concentration (usually to <2.2 mmol/L). The insulin-induced hypoglycemia triggers the release of ACTH from the pituitary gland[65] and, subsequently, cortisol from the adrenal cortex.[66] Several investigators have provided clinical evidence[33,67,68] of the similarity of plasma cortisol responses to insulin-induced hypoglycemia and to surgery. In a review of 6580 insulin tolerance tests[59] Fish and colleagues found only six cases with untoward side effects (two episodes each of coma, angina, and impending seizure). All were reversed with intravenous glucose administration. The insulin tolerance test must be performed in a standard, closely monitored setting.

Kehlet and colleagues[23,34,36,38,57,69,70] have provided convincing evidence that the 30-minute ACTH test is the most convenient and accurate diagnostic tool for preoperative evaluation of HPA axis function. Synthetic ACTH (Cortrosyn, Cosyntropin), in a dose of 250 μg, is administered intravenously, and a blood sample for plasma cortisol is collected 30 minutes later. Traditionally, a plasma cortisol concentration of >500 nmol/L (18–20 μg/dl) defines adequate adrenal function.

The ACTH stimulation test has a close correlation with the insulin tolerance test ($r = 0.92$; $p < 0.0001$).[69]

Some authors have noted discordant results between the two tests in patients with acute pituitary disorders.[71,72] Lindholm and Kehlet studied 200 patients with suspected hypothalamic-pituitary disorders and found a correlation between the two tests ($r = 0.83$; $p < 0.0001$).[73] They again confirmed the close correlation between the insulin tolerance and ACTH stimulation tests. They noted that discordant results can be obtained in an initial 1- to 2-week period after acute ACTH deprivation (pituitary surgery), a finding that can explain the normal cortisol response to ACTH in patients with acute pituitary disorders.[71,72] We advocate use of the ACTH stimulation test as a preoperative screening test for evaluation of HPA integrity.

PRESCRIBING PERIOPERATIVE GLUCOCORTICOID COVERAGE

In a review of glucocorticoid therapy, Axelrod states that anyone who has "received a glucocorticoid in doses equivalent to 20 to 30 mg of prednisone per day for more than a week should be suspected of having HPA suppression."[74] Thus, the need to evaluate the HPA axis is a frequent consideration. Determining the actual need for glucocorticoid coverage is desirable and appropriate. The clinical complications of glucocorticoid therapy are reviewed elsewhere.[75] Special concerns about glucocorticoid use in surgical patients include the potential for adverse effects on wound healing,[76] immune function,[77–79] and interaction with nondepolarizing, neuromuscular antagonists.[80–81]

If biochemical evaluation demonstrates inadequate HPA axis function (i.e., an abnormal ACTH stimulation test), or if no preoperative testing is performed, perioperative glucocorticoid coverage should be provided. In urgent or emergent situations, the physician usually must rely on the physical signs of Cushing's syndrome that correlate with HPA axis suppression in glucocorticoid-treated patients and nonspecific laboratory information suggestive of adrenal dysfunction, such as hyponatremia and eosinophilia (indicative of the possibility of adrenal insufficiency).

The question remains — how much glucocorticoid, how often, for how long, and via what route of administration? A clue to the appropriate glucocorticoid replacement dosage is provided by the normal cortisol secretion rate in response to surgery. Kehlet[23] estimates that adults secrete 75–150 mg a day in response to major surgery and 50 mg a day during minor procedures. Table 2 reviews the available data on cortisol secretion rates and major surgery. We conclude from these data that cortisol secretion in the first 24 hours after surgery rarely exceeds 200 mg. Additionally, the secretion rate seems to parallel the duration and extent of surgery. There are no data supporting the concept that exceeding this amount of glucocorticoid administration is ever beneficial.

Prior Therapeutic Strategies

Kehlet's[82] recommendations for perioperative glucocorticoid coverage are based on the normal cortisol response to surgical stress. In long-term glucocorticoid-treated patients scheduled for major surgery, Kehlet[82] recommends 25 mg of intravenous cortisol, or its equivalent, with induction of anesthesia and 100 mg given by continuous infusion over the next 24 hours. An alternative is 25 mg of cortisol equivalent given as an intravenous bolus (over 10–20 minutes) every 4 hours. After minor surgery, he recommends that the usual oral glucocorticoid replacement dose be reinstated immediately after the operation.

Lloyd[83] suggests minimal coverage with supplementation only if postoperative hypotension occurs. Plumpton and co-workers[84] showed that 100 mg of intramuscular hydrocortisone hemisuccinate administered every 6 hours resulted in plasma cortisol concentrations similar to those values in normal subjects undergoing similar operative stress. Gran and Pahle[85] administered a single intramuscular injection of depot betamethasone (Celestone chronodose) to glucocorticoid-treated patients. In their study, patients receiving glucocorticoids up to the time of surgery were given 2 mL of the depot agent (equivalent to 400 mg cortisol) for major surgery and 1 mL for minor surgery.[85] The agent had effects lasting up to 6 days from one injection.[84]

Postoperatively, Kehlet[23,82] recommends an intravenous infusion of cortisol equivalent (100 mg/24 hours dissolved in 500–1000 mL of isotonic saline), using return of gastrointestinal function as the indicator for return to the preoperative regimen. Although it has been customary to reduce the quantity of glucocorticoid coverage gradually over a period of days during the postoperative period, there is little evidence to support the practice, except in cases of high-dose glucocorticoid administration for prolonged periods. If HPA axis suppression is suspected postoperatively, the ACTH stimulation test will establish the diagnosis.[53,89]

NEW RECOMMENDATIONS FOR GLUCOCORTICOID COVERAGE

We believe that glucocorticoid administration during stress should be based on the magnitude of the stress and the known glucocorticoid production rate associated with it. For **minor surgical stress** (i.e., inguinal herniorrhaphy) the daily cortisol secretion rate and static plasma cortisol measurements[24–25] suggest that the glucocorti-

Table 2. CORTISOL SECRETION RATE FOLLOWING MAJOR SURGERY— THE OBSERVATIONS OF VARIOUS INVESTIGATORS

Authors	Year	Cortisol Secretion Rate	Comments
Hardy and Turner[32]	1957	111 mg/24 hrs	Done by adrenal vein catheterization Constant secretion rate assumed Venous outlets overlooked 10 patients studied
Hume et al.[39]	1962	95 mg/24 hrs	Done by adrenal vein catherization Constant secretion rate assumed Venous outlets overlooked 7 patients studied with indwelling adrenal vein catheters
Wise et al.[105]	1975	60 mg/24 hrs	Estimated from repeated plasma cortisol determinations Assumes a constant distribution volume for cortisol 3 patients studied
Kehlet and Binder[57]	1973	10 mg/hour immediately postoperative 5 mg/hr 24 hrs later 75–150 mg/24 hrs	Used ^{3}H cortisol before and then 2, 10, and 24 hrs after skin incision 4 patients studied
Peterson et al.[106,107]	1959–1960	167 mg/24 hrs Range 116–200 mg/24 hrs	Examined plasma clearance in 5 normal subjects
Ichikawa[108]	1966	93 mg/24 hrs 156 mg/24 hrs	Measured cortisol secretion in 2 normal subjects
Thomas et al.[109]	1971	222 mg/24 hrs Range 135–310 mg/24 hrs	9 asthmatic patients in which maximal cortisol secretion was studied Assumed steady state. Overestimate likely

coid target is about **25 mg of hydrocortisone equivalent.** For example, a patient receiving 5 mg of prednisone every other day for asthma who is scheduled for an inguinal hernia repair should receive preoperatively 5 mg of prednisone, with both the surgeon and anesthetist aware of the possible complications. If the postoperative course is uncomplicated, the patient can be returned the next day to his/her usual glucocorticoid dosage.

For **moderate surgical stress,** (i.e., nonlaparoscopic cholecystectomy, lower extremity revascularization, segmental colon resection, total joint replacement, abdominal hysterectomy), cortisol production rates suggest the glucocorticoid target is about **50 to 75 mg per day of hydrocortisone equivalent for 1 to 2 days.** For example, a patient receiving 10 mg of prednisone for systemic lupus erythematosus should receive 10 mg of prednisone (or parenteral equivalent) preoperatively and 50 mg of hydrocortisone administered intravenously intraoperatively. We suggest that 60 mg of hydrocortisone (20 mg every 8 hours) be administered intravenously on the first postoperative day and that patients return to their preoperative glucocorticoid doses (enterally or parenterally) on postoperative day 2.

Finally, for **major surgical stress** (pancreatoduodenectomy, esophagogastrectomy, total proctocolectomy, cardiac surgery involving cardiopulmonary bypass) the glucocorticoid target should be **100 to 150 mg of hydrocortisone equivalent per day for 2 to 3 days.** A patient with ulcerative colitis who has been receiving 40 mg of prednisone daily for several years who is scheduled for major surgery (e.g., total proctocolectomy), should receive 40 mg of prednisone (or the parenteral equivalent) preoperatively (within 2 hours of surgery), and 50 mg hydrocortisone intravenously every 8 hours after the initial dose for the first 48 to 72 hours after surgery. As a second example, a patient with arthritis who has been receiving 5 mg of prednisone daily and who is undergoing similar major surgery should require 5 mg oral prednisone (or the hydrocortisone equivalent intravenously) as a preoperative dose, with 25 mg of hydrocortisone to be given intraoperatively, and 25 mg to be administered in the 8 hours after surgery. Over the subsequent 48 hours, we would prescribe 25 mg of hydrocortisone every 8 hours. The examples provided for major surgical coverage demonstrate our belief that the provision of perioperative glucocorticoid coverage must account for the patient's preoperative glucocorticoid dose and the duration and severity of surgery or other stress.

To our knowledge, there are no data that indicate these recommended equivalent doses need to be exceeded. Thus, the patient who is receiving a maintenance dose of glucocorticoid therapy that exceeds the estimated stress requirement will not need more glucocorticoid coverage during the stress period. After uncomplicated major sur-

gery, plasma cortisol concentrations decrease rapidly. The circulating cortisol concentration is normal by 24 to 48 hours after surgical stress in most patients.[22,87,88] A postoperative increase in cortisol secretion is presumptive evidence for a continued or new stressor (i.e., fever, peritonitis, etc.). In the case of postoperative complications, we recommend continued glucocorticoid administration consistent with the postoperative stress response.

THE FUTURE

Although the HPA response to stress is well defined and Addisonian patients or adrenalectomized animals succumb to stress, the precise physiologic roles of glucocorticoids in meeting the demands of stress are unknown. We believe that recent work[90–104] has begun to identify the mechanisms by which glucocorticoids exert their actions during stress. Some of this work has focused on the relationship of and communication between the immune system (lymphocyte and macrophage-borne cytokines) and the HPA axis.

Woloski and colleagues[90] provided experimental evidence that monokines, such as interleukin-1 (IL-1), when added to cultures of mouse pituitary tumor cells and adrenal cells, stimulate the release of ACTH and glucocorticoids. They suggest that increases in IL-1 during states of inflammatory/immune response (stress) may be responsible for activation of the HPA axis, and hypothesized that a feedback loop exists between the immune system (monokines) and the HPA axis. Other investigators have noted IL-1-induced secretion of ACTH by rat pituitary cells.[89–90] Besedovsky and co-workers[93] showed that infusions of IL-1 in mice were associated with increased blood levels of ACTH and glucocorticoids. Further, these investigators and others[93–96] suggest that corticotropin-releasing factor modulates the IL-1-induced pituitary adrenal activation. Recent experimental evidence suggests that interleukin-6 is a potent stimulus for release of ACTH *in vitro*[97] and *in vivo*.[98]

Infusions of tumor necrosis factor (TNF) cause sustained increases in circulating glucocorticoid concentrations in rats[99] and dogs.[100] Adrenalectomized rats have a 100% mortality rate from such an infusion.[99] Pre-treating these animals with dexamethasone (0.3 mg/kg) prevents death from TNF or IL-1 infusions[101] and inhibits endotoxin-induced TNF release.[102]

Marano and colleagues[103] measured TNF and serum cortisol concentrations in patients with severe burn injury. In 16 patients studied longitudinally, they found that cortisol levels are significantly higher ($p < 0.02$) in the absence of detectable circulating levels of TNF.[103] They suggest that high cortisol levels may interfere with cytokine production.[103] Naito and co-workers[104] longitudinally evaluated circulating ACTH, cytokines (TNF, IL-6), and cortisol concentrations in patients undergoing pancreatoduodenectomy or total joint replacement procedures. They showed that (in pancreatoduodenectomy patients) significant intraoperative and postoperative increases in circulating cytokine concentrations were related temporally to elevations in postoperative cortisol values in the first 48 to 72 hours after surgery.[104] These studies suggest a connection between the stress response and the pro-inflammatory cytokines. Further studies should define the effect of glucocorticoids (during surgery/stress) as counterregulatory hormones modulating the release or modifying the systemic actions of cytokines.

Four decades have passed since a standard of care was established for perioperative glucocorticoid coverage. This initial standard was based on anecdotal information. Experimental data accumulated since that time support the concept that new recommendations are in order. This article provides a framework for those new recommendations in the context of the need to individualize this important aspect of pharmacologic management.

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